



Residents' Case Series

Case Report

The patient was a thirty-five-year-old Vietnamese woman who was previously healthy. She presented to her primary care physician with a chief complaint of fever, severe genital pain and polyarthralgia. She first noticed dyspareunia approximately six weeks prior to this presentation. Then, three weeks prior to presentation, the patient developed fever as well as vaginal pain upon ambulation and urination. She also noticed some vaginal and oral pustules, which were cultured and found to be positive for herpes simplex virus. She was treated with a ten-day course of valacyclovir 1000 mg twice daily by mouth. However, she described spreading vesicles and pustules from her vagina to her legs bilaterally two weeks prior to this presentation, with severe pain requiring pain medication. One week prior to this presentation she also developed multiple migratory joint pains in her knees, fingers and toes with warmth and swelling.

The patient denied any history of sexually transmitted diseases and had only one sexual partner. Her past surgical history included bilateral breast augmentation. She was a nonsmoker and a social drinker on rare occasions. The patient's family history was significant for lung cancer in her father and breast cancer in her mother.

On physical examination she appeared younger than her stated age and was in moderate distress secondary to pain. She had a temperature of 100.2 F, a blood pressure of 100/70 mmHg, and a heart rate of 72 beats per minute. She had multiple erythematous-based papular lesions scattered on her back, legs and under the left breast. Several of which had erupted with necrotic centers. These lesions were tender to touch. There were multiple shallow irregular ulcers on the buccal mucosa and on upper and lower gums, some of which were confluent. She had marked bilateral vulvar and labia majora ulcers and swelling with profuse, non-foul smelling, purulent, creamy yellow blood-tinged discharge. There was swelling, erythema and tenderness of bilateral wrists, feet, ankles and the first metatarsophalangeal joints. The remaining joints appeared normal.

Diagnostic data showed a complete blood count with 16.1×10^9 white blood cells (WBC) with 88% neutrophils, 10% lymphocytes and 2% monocytes, hemoglobin of 13.4 g/dL, hematocrit of 38.1%, and a platelet count of 446×10^9 /L. The abnormal chemistries (and normal values) were as follow: sodium 133 mEq/L (136-146), gamma GT 70 IU/L (10-66), globulin 5.0 g/dL (2.7-4.0) and erythrocyte sedimentation rate >130 mm/hr (0-20). The urinalysis showed 20-50 WBC/high power field (HPF) and 5-20 RBC/HPF with negative nitrite and leukocyte esterase and a no growth urine culture. Rheumatoid factor, anti-nuclear antibody titer and rapid plasma reagin (RPR) results were negative. Her C3 and CH-50 complements were elevated at 224 mg/dL (80-200) and 324 units (101-300), respectively, whereas the C4 complement level was normal at 37 mg/dL (15-50). The serology tests for HIV, chlamydia and gonococcal antibodies were all negative.

The patient also underwent arthrocentesis of the left knee joint with synovial fluid analysis as follow: lactate dehydrogenase (LDH) 187 IU/L, protein 4.2 gm/dL, glucose 73 mg/dL. The microscopic

A Thirty-five-year-old Woman with Oral and Genital Ulcers, Pustular Skin Lesions, and Polyarthrititis

Thitinan Srikulmontree MD,
Paranec Auethavekiat MD, and David John MD

examination showed 9,900 WBCs per cu.mm. (62% neutrophils, 6% lymphocytes and 32% monocytes), and 600 RBCs per cu.mm. There were neither crystals nor fibrin clots observed.

The patient was hospitalized for the above presentation. She was treated empirically with intravenous ceftriaxone and acyclovir for presumed gonococcal and herpes simplex infections. However, she continued to have multiple pustular skin lesions and therefore ciprofloxacin was added to the regimen for the possibility of resistant strain of gonococcal infection. Her symptoms then partially improved and the patient underwent skin biopsies from the left ankle and mid back. The results of which showed superficial and deep perivascularitis with mixed inflammatory cell infiltrate including neutrophils and eosinophils with vasculitis involving one dermal blood vessel and with acute and chronic perifolliculitis. Subsequently, her condition slowly improved with resolution of the oral and genital ulcers, although the polyarthrititis and arthralgias persisted. It was also noted that throughout the hospitalization the patient had multiple pustular lesions appearing at sites where she had had venipunctures, which resulted in multiple restarts of intravenous access.

Discussion

This patient presented with multiple organ involvements suggesting a systemic condition as an etiology. The finding of pustular eruptions at the venipuncture sites, also known as pathergy equivalent reaction, is highly suggestive of Behcet's disease.

Behcet's disease is a chronic multisystemic disease of uncertain pathogenesis characterized by oral and genital aphthae, arthritis, cutaneous lesions, and ocular, gastrointestinal, and neurologic manifestations.¹ The Turkish dermatologist, Hulusi Behcet, first described it in 1937 as a disease of "recurrent oral aphthous ulcers, genital ulcers, and hypopyon-uveitis."² The diagnosis of Behcet's disease is based on clinical criteria as established by O'Duffy and Goldstein³ and the International Study Group.⁴ Complex aphthosis, as defined by Jorizzo et al,⁵ is the presence of almost constant, multiple (≥ 3) oral or oral and genital aphthae in the absence of systemic manifestations. These patients must be distinguished from those with Behcet's disease. Complex aphthosis can be seen with vitamin B1, B2, B6, B12, folate, iron, and zinc deficiencies that respond to replacement therapy.⁶⁻⁷ Other etiologies of aphthosis include hematologic abnormalities such as cyclic neutropenia and agranulocytosis;⁸⁻⁹ allergies to various food including cow's milk, gluten, food dyes, and preservatives;¹⁰⁻¹¹ nonsteroidal anti-inflammatory drugs;¹² sodium lauryl sulfate, used in dentifrices;¹³ systemic

diseases such as inflammatory bowel disease, Sweet's syndrome, and HIV;¹⁴⁻¹⁶ herpes simplex infection and impaired cell-mediated immunity.¹⁷⁻¹⁸

The pathergy test is currently applied with a disposable 20- or 22-gauge needle, penetrated obliquely to a depth of about 5 mm. A positive test result is the presence of an erythematous papule >2 mm at the entry site, which is read at 48 hours. It is an important test in the diagnosis of Behcet's disease.¹⁹ Clinical evaluation of the pathergy test is sufficient for both the diagnosis and is useful in assessing the activity of Behcet's disease. Prior studies have shown that histopathologic evaluation of the test is not recently more sensitive than the clinical evaluation in general.²⁰ However, due to poor reproducibility of the clinical pathergy test, Jorizzo et al. proposed the use of histopathologic examination of histamine injection sites instead of clinical evaluation.²¹⁻²² Their result showed a strong association between positive histopathologic pathergy testing and active Behcet's disease in all 9 patients who entered the study. This diagnostic investigation method still needs further comparison study with the standard pathergy skin test.

Different positive pathergy reaction rates in Behcet's disease have been reported worldwide. While this test is usually positive in most patients from the Middle and Far East, it is less often positive in patients seen in North America or East India.¹⁹ The presence of a positive pathergy reaction is not associated with an increased risk for specific mucocutaneous or systemic manifestations of the disease, and probably does not predict a more severe disease course.²³

Although the etiology of Behcet's disease is still unknown, recent studies suggest possible correlation between the disease and an infectious etiology. The heat shock protein (HSP), a specific protein found in several bacteria including a streptococcal 60kd HSP as well as several mycobacterial HSP-65 peptides and their human analogues (HSP-60) have been shown to stimulate a lymphoproliferative response in patients with Behcet's disease in a specific manner.²⁴⁻²⁷

A stronger association may be that of herpes simplex virus infection and Behcet's disease. There is evidence of herpes simplex virus type 1 (HSV 1) DNA isolation from nuclei of peripheral blood lymphocytes in patients with Behcet's disease, but the findings are inconsistent. In one study, biopsied specimens from ulcers of 21 patients with recurrent aphthous stomatitis were detected with HSV 1 in 6 patients, although neither varicella-zoster virus (VZV) nor cytomegalovirus (CMV) was isolated. HSV probably does not induce the disease through classic immunopathological mechanisms, but rather as a promoter of abnormal lymphoproliferation in individuals with predisposing defects, possibly related to selective DNA repair defects.²⁸ Markedly impaired CD4 cell response to HSV 1, but not CMV nor VZV, was found in patients with Behcet's disease as well as patients who had recurrent herpetic infections, known to be caused by latent HSV 1 infections. A similar, but less dramatic result was found in the impairment of CD8 response in the same patient group.²⁹

Our case report had a positive HSV culture from her genital ulcers, as well as clinical manifestations of Behcet's disease with a partial clinical response to treatment with multiple antimicrobial medications. Studies on several immunosuppressants and acyclovir have shown variable response. A recent and promising study by Shon et al. has shown significant improvement of Behcet's disease symptoms as well as preventing recurrence in HSV-induced Behcet's

disease mice when famciclovir was given from the appearance of lesions, whereas neither pretreatment nor concurrent treatment at the same time of HSV inoculation found to be effective.³⁰

In summary, a diagnosis of Behcet's disease is often difficult to make. There are no specific pathologic or serologic tests. The clinical manifestations of Behcet's disease often overlap with that of other systemic diseases. Cutaneous pathergy reaction is a useful and important sign and should always raise a clinical suspicion of the disease. The presence of HSV infection can also be found concomitantly, and may play a role in the immunopathogenesis of the disease. This should lead to further investigations in a more specific treatment such as an antiviral regimen.

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